REMARKS

Receipt of the Office Action mailed October 26, 2007 is acknowledged. Claims 1-22, 61, and 62 are pending. Claim 1 is amended to further clarify the fact the forming step and the hydration step are performed without the addition of PEG. Support for this claim amendment can be found on page 7, lines 7-11 of the originally filed application and throughout the specification where the term "non-pegylated" liposomes is used and in the examples showing manufacture of liposomes without the addition of PEG. Accordingly, no new matter is being added through this claim amendment. Claims 9, 23-60 were previously canceled. Applicants reserve the right to pursue claims 23-60 through one or more divisional applications. Reconsideration in view of the above amendments and following remarks is respectfully requested.

Claim Rejections - 35 U.S.C § 103(a)-Kirpotin

The Examiner maintains the rejection of claims 1-8, 10-22 and 61 under 35 U.S.C § 103(a) as being unpatentable over Kirpotin (U.S. Patent No. 6,110,491).

Evidence of Unexpected Results Must Be Weighed

Applicants respectfully submit that the Examiner has failed to properly consider the Declaration of Mr. Pai (referred to by the Examiner as Mr. Annappa) dated October 18, 2007. Assuming, *arguendo*, the Examiner previously established a *prima facie* case of obviousness, Applicant may rebut such a *prima facie* case by providing a "showing of facts supporting the opposite conclusion." *In re Piasecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984). Rebuttal evidence may show, for example, that the claimed invention achieved unexpected results relative to the prior art. *In re Geisler*, 116 F.3d 1465, 1469-70, 43 USPQ2d 1362 (Fed. Cir. 1997). Such secondary considerations are considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art. *Id.* Such a showing dissipates the *prima facie* holding and requires the examiner to consider all of the evidence anew." *Id*; *See also In re Rinehart*, 531 F.2d 1048, 1052, 189 USPQ 143 (CCPA 1976).

Presently, the declaration of Mr. Pai rebutted any showing of obviousness by demonstrating both Kirpotin's failure to teach or even suggest the production of non-pegylated liposomes as recited in claim 1 as well as the unexpected pharmacokinetic results as a result of a

decreased introduction of hydration media. The Examiner was required to have at least weighed the evidence provided in the Declaration and provide an explanation of why such results were not, in fact, unexpected before making a final determination of the obviousness of the claimed invention. *See In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978); *see* MPEP 716.02(c)("Evidence of unexpected results must be weighted against evidence supporting prima facie obviousness in making a final determination of the obviousness of the claimed invention").

Furthermore, the Examiner has also offered no factual evidence to support his statement that Kirpotin teaches or suggests non-pegylated liposomes (*i.e.* making liposomes without the addition/use of PEG), much less makes obvious the use of an "amount of aqueous hydration media used is in the range of 10 to 35 ml for each mmole of phospholipid present in the lipid solution." The Examiner is required to produce the factual basis for the rejection. *In re Warner,* 379 F.2d 1011, 1016, 154 USPQ 173, 177 (CCPA 196). The Examiner by making a blank statement without any factual support is holding himself out as an one skilled in the art, which is improper. Presently, the Examiner fails to point to any place in Kirpotin that teaches or even suggests the production of non-pegylated liposomes, much less any factual evidence showing why reduced toxicity upon loading due to decreased introduction of hydration media is not unexpected.

For the reasons set forth above, Applicants respectfully request the Examiner consider the Declaration and the factual evidence it provides before making any further determination regarding obviousness.

Remarks Regarding the Rejection

Applicants previously submitted a section 1.132 Declaration of Pai Srikanth Annappa demonstrating, *inter alia*; (1) Kirpotin simply does not teach or suggest a process for the manufacture of long circulating non-pegylated liposomes as set forth in claim 1 (see paragraph 7 of declaration of Mr. Annapa), (2) unexpected results in that one of ordinary skill would not expect that by simply reducing the amount of hydration buffer, one would obtain a stable liposome without the need for PEG (see paragraph 9 of Declaration of Mr. Pai); and (3) no one would be motivated to even consider Kirpotin for suggesting a non-pegylated liposome made by reducing the amount of hydration buffer (see paragraph 10 of declaration of Mr. Pai). Thus,

Applicants have rebutted any evidence of obviousness by fully establishing that Kirpotin does not even teach or suggest that one could remove PEG to make a rigid stable liposome, much less a utilizing a lower amount of hydration media than what had previously been thought as the optimum amount of hydration media to use.

The Examiner contends that Applicant's "argument is not persuasive since Kirpotin teaches the method of preparation of non-pegylated liposomes." (page 3, lines 5-7 of Office Action dated October 26, 2007). Applicants have previously established, though the Declaration of Mr. Pai, that Kirpotin does not teach the preparation of non-pegylated liposomes. In furtherance of this fact, Applicants respectfully direct the Examiner's attention to the language of Examples 1-9. Specifically, Example 1 states:

> 21.6 mg of polyacrylic acid (molecular weight 2,000; Aldrich Corporation, Milwaukee, Wis.) were dissolved in 3 ml of water and neutralized to pH 7.4 with NaOH to produce 100 milli-eq/L sodium polyacrylate solution. 10 mg of the mixture of egg PC, cholesterol, and PEG (molecular weight 2,000)-DSPE (Avanti Polar Lipids, Birmingham, Ala.) in the molar ratio of 10:5:1 was dissolved in chloroform, the solvent was evaporated in vacuum, the lipid film was incubated with shaking in 1 ml of the above polyacrylate solution, and the lipid dispersion was extruded under pressure through 2 stacked Nucleopore (Pleasanton, Calif.) membranes with pore size 0.2 μmol.

(see column 12, lines 7-18)(emphasis added).

Example 2 utilizes "a solution of free doxorubicin or the doxorubicin liposomes described in Example 1." (see column 12, lines 46-47). Example 3 states that the "[l]iposomes were prepared as in Example 1, except that inner buffer, instead of polyacrylic acid, contained 5 mg/ml of chondroitinsulfate A ..." (see column 12, lines 66-column 13, line 1). Example 4 states that the "[l]iposomes were prepared from egg phosphatidylcholine using the procedure identical to Example 1" with different buffers in place of polyacrylic acid. (see column 13, lines 13-14). Example 5 states that "[l]iposomes were prepared and loading with doxorubicin as in Example 4, except that prior to drug loading, nigericin was added to the liposomes at a concentration of 5 μmol/L." (see column 13, lines 37-39). Example 6 states that the "[l]iposomes were prepared as described in Example 1..." (see column 14, lines 4-5). Example 7 states:

> Liposomes with entrapped ammonium sulfate or ammonium polyacrylate were prepared from the lipid mixture of hydrogenated soybean phosphatidylcholine

> (Avanti PolarLipids, Ala., U.S.A.), cholesterol (Calbiochem, USA), and poly(ethylene glycol) (Mol. weight 2,000) derivative of distearoyl phosphatidyl ethanolamine (PEG-DSPE) (Sygenta, Switzerland), at the molar ratio 60:40:6, by lipid film hydration, repetitive freezing-thawing at 60°C. (6 times) and extrusion through two stacked polycarbonate track-etched membranes with the pore size 100 nm at 60°C. (12 times).
>
> (see column 14, lines 17-27)(emphasis added).

Example 8 states:

> [l]iposomes containing entrapped ammonium salt solutions as above were prepared from egg phosphatidyl choline, cholesterol, and PEG-DSPE as described in the Example 7, except that lipid hydration and extrusion were carried out at room temperature.

(emphasis added)

In Example 9, "[d]oxorubicin hydrochloride was added to the aliquots of Inner Buffers described in Example 8." Thus, all Examples describe pegylated liposomes – that is all of the of the examples show that the liposomes contain PEG. Further, there is no discussion in the specification relating to making a liposome without using PEG. This is not surprising as Kirpotin is directed to loading a liposome with higher density and has nothing to do with making a long-circulating liposome.

Further, the Examiner has refused to consider the unexpected results discussed in Mr. Pai's Declaration because the tests were performed on commercially available liposomes and not the liposomes of Kirpotin. The key point is that both the commercially available liposomes and the liposomes taught in Kirpotin are made with PEG (in contrast to the presently claimed liposomes not being made with PEG). Hence, the comparison is valid. The unexpected results of the presently claimed liposomes are achieved by creating a long lasting and stable liposome without the use of PEG in the liposomes, created in part by using less hydration media in the hydration step than previously known. Thus, the unexpected results seen in the presently claimed liposomes need only be unexpected over pegylated liposomes (liposomes made with PEG). The Declaration and the specification report the results of tests comparing liposomes made by the present invention (made without PEG using less hydration media in the hydration step) against liposomes made with PEG. As the present specification demonstrates, PEG had been

traditionally used to provide stability so comparison with any pegylated liposome was proper. Thus, the comparison was proper and the Examiner has erroneously not considered Mr. Pai's Declaration providing unexpected results. Accordingly, applicants request that the Examiner consider the Declaration.

Further, applicants submit that the Examiner is using impermissible hindsight to find the present invention obvious. The Examiner has repeated his argument that it would have been obvious to reduce the amount of hydration media. Where in the prior art does it show or even hint that one could reduce the amount of hydration media to the recited range ("wherein the amount of aqueous hydration media used is in the range of 10 to 35 ml for each mmole of phospholipid present in the lipid solution') to allow one to make a long-circulating stable liposome without using PEG? In addition, where in the cited prior is there a discussion about making a non-pegylated liposome to provide a long-circulating stable liposome that is comparable to, or even less toxic than, a pegylated liposome? Where in the prior art is there any discussion on how to achieve such a liposome? Applicants respectfully submit that the cited prior art simply does not address any of these issues nor suggests how to achieve such liposomes. Thus, there is no motivation to make a liposome without PEG by using the recited amount of hydration media (less than what was normally used) to achieve a long-circulating stable liposome. Applicants submit that the Examiner has used impermissible hindsight and knowledge of the present invention to arrive at his decision of obviousness. As such, Applicants respectfully requests withdrawal of this ground of rejection.

Claim Rejections - 35 U.S.C § 103(a)-Forssen/Janoff

The Examiner rejects claims 1-8, 10-22 and 61-62 under 35 U.S.C §103(a) as being unpatentable over Forssen (5,714,163) in combination with Janoff (4,880,635). As noted in the previous response, neither Forssen nor Janoff teach or suggest a process for the manufacture of long circulating non-pegylated liposomes as set forth in claim 1. Secondly, one skilled in the art would not be motivated to even consider Forssen or Janoff for suggesting a nonpegylated liposome made by reducing the amount of hydration buffer. Furthermore, the declaration of Mr. Pai submitted with the last response clearly demonstrated unexpected results in that one of

ordinary skill would not expect that by simply reducing the amount of hydration buffer, one would obtain a stable liposome without the need for PEG.

In addition, Janoff teaches liposomes that are required to be dehydrated and then rehydrated to achieve long-term storage without substantial loss of their internal contents. Janoff does not teach in the preparation of liposomes that sugar is required to be added in the hydrating buffer along with Ammonium sulphate (as required by the present claims).

Further, Janoff describes a method of preparing liposomes by mixing drugs with phospholipids but also does not use ammonium sulphate in the hydration medium. How can this be considered as motivating to combine with Forssen and arrive at a process of preparing liposomes not containing drugs, incorporating ammonium sulphate and sucrose in limited defined amounts of hydration medium?

Accordingly, Applicant respectfully submits that Forssen and Janoff, alone or in combination, do not teach or suggest each and every element of the claims and accordingly submits that claims 1-8, 10-22 and 61-52 are patentable under 35 U.S.C § 103(a). Applicant respectfully requests withdrawal of this ground of rejection.

CONCLUSION

No additional fees are believed to be owed at this time. However, in the event that additional fees are required, the Commissioner is hereby authorized to charge Womble Carlyle Sandridge & Rice, PLLC Deposit Account No. 09-0528, or credit any overpayments to this account.

The Examiner is invited and encouraged to contact the undersigned at 703/394-2273 to discuss any matter in this application.

Respectfully submitted,
Womble Carlyle Sandridge & Rice, PLLC

Date: October 31, 2007

For Teresa A. Lavenue Reg No 59,566
Registration No. 47,737
Phone: (703) 394-2273
Fax: (703) 790-2623
Email: tlavenue@wcsr.com

P.O. Box 7037
Atlanta, GA 30357-0037
Customer No.: 26158